Improving Risk Assessment Through The Use of Physiologically-Based Models

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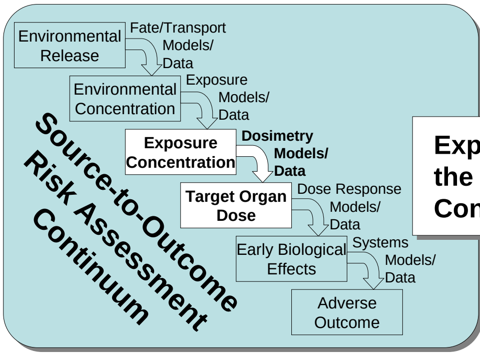
EPA Science Forum 2004
Healthy Communities and Ecosystems

I. Differences in chemical disposition may lead to different biological effects for the same exposure.

- The same external exposure may lead to different effects in different species or between different individuals.
- Some of these differences may be due to differences in pharmacokinetics – the movement of the chemical through the body, including differences in:
  - – Absorption into the body
  - – Distribution to and within various tissues
  - – Metabolism into other chemical species
  - – Excretion from the body
- These “pharmacokinetic” differences can change how much chemical reaches the site where it is biologically active (i.e., the target/organ dose).

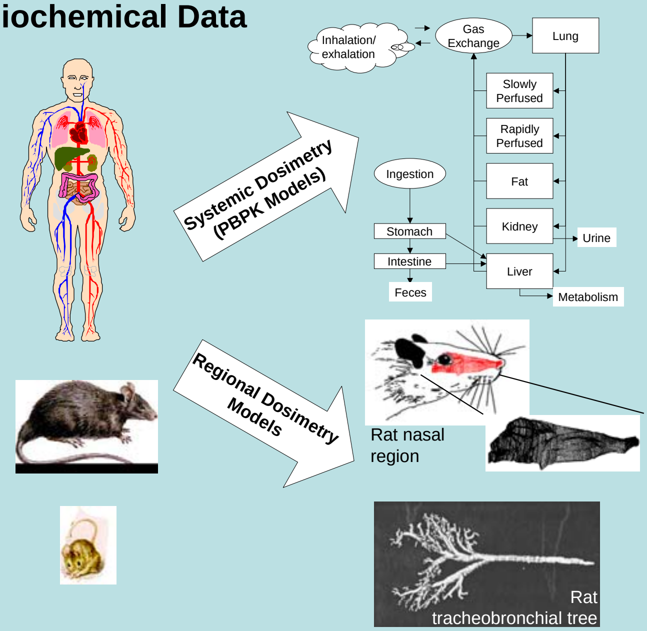
II. Examples of physiologically-based models that simulate chemical kinetics.

- Whole Body PBPK Models
  - – Whole body Physiologically-Based Pharmacokinetic (PBPK) Models represent organs and tissues with a series of interconnected compartments, and have been developed for a wide range of chemicals.
- Local Models (when regional dosimetry is needed)
  - – Computational Fluid Dynamics (CFD) model for the oro-nasal region (e.g., formaldehyde, particulate matter).
  - – Lung models with single/multiple path idealizations (e.g., particulate and fibrous matter, ozone, formaldehyde).
  - – May be integrated with PBPK models.
- All models require substantial physiological and biochemical data to implement.



Exposure-to-Dose part of the Source-to-Outcome Continuum

Physiological and Biochemical Data | **Mathematical Models**



III. EPA develops, evaluates, and applies physiologically-based models in risk assessment.

- Models have been developed for many chemicals, including: Dioxin, Methylene Chloride, Vinyl Chloride, Ethylene Dichloride, Chloroform, Trichloroethylene, Tetrachloroethylene, Formaldehyde, Ozone, Particulate Matter.
- Ongoing efforts to enhance use of these models include:
  - – Report on PBPK models in risk assessment with illustrative case studies;
  - – Development of standardized, peer-reviewed parameters across life stages;
  - – Peer review of existing models, and development of new or modified models;
  - – Training on the use of models for EPA and non-EPA risk assessors;
  - – Databases of PBPK and dosimetry models and parameter values.
- Multiple ORD centers and laboratories, including NCEA, NERL, and NHEERL, collaborate in this effort.

Uncertainty and Variability in Physiologically-Based Models

- Uncertainties in models can arise out of
  - – Model errors and data gaps
  - – Measurement errors and analytical uncertainties
- Inter- or intra-species variability in kinetics may be due to differences in:
  - – Physiology (e.g., body weight, % body fat, organ sizes, shapes)
  - – Variation (e.g. genetic) in metabolism and biochemistry
  - – Co-exposures to other chemicals (e.g., alcohol)
  - – Disease states
- Population pharmacokinetic models can help characterize uncertainty and variability.

IV. Physiologically-based models increase the accuracy and completeness of EPA risk assessments by improving their ability to:

- Focus on the most relevant/most accurate dose-metrics.
- Predict the internal doses for different routes of exposure, different species, different age groups or genders, and other sources of variability
- Characterize and reduce uncertainty
- Predict responses from mixtures of chemicals
- Integrate with biologically-based dose-response (BBDR) models.